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CONCERNING THE PATHOGENESIS OF RELAPSES IN MALARIAL FEVERS.*

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As is known, since the researches on the cycle of the malarial parasites in anophelene mosquitoes, the problem of the treatment of malaria has assumed a very great social importance, considering that the specific treatment of human illness represents a method of social prophylaxis to which is given more trust than to any other.

But anyone who has a knowledge of malaria knows the difficulties which are not seldom encountered in the task of treating obstinately relapsing infections. It is not unusual to observe sick persons who, after a long series of relapses, have become so skeptical in regard to the efficacy of quinine that they refuse to continue taking the remedy.

And inasmuch as various facts bring me to the belief that the relative resistance of relapsing malarial infections to the valuable drug may be in intimate relation with the pathogenic mechanism of such infections, I think it is of advantage, on account of the practical importance of my argument, to explain certain considerations bearing on these facts,. although I may not deal in great part with anything new.

It is almost useless to call attention to the fact that one of the most debated and obscure questions in the pathology of malaria is precisely that which concerns the genesis of relapse; these, as every one knows, are found in all kinds of malarial infections, sometimes separated by brief intervals of apyrexia, sometimes by long periods of latency.

It is also known that relapses may happen one after the other with a certain regularity. For in sick persons who take quinine only in sufficient quantity to cause a cessation of the fever, and who then suspend the use of the drug, it is especially observed that relapses return at intervals a little short of two weeks; intervals, as I have noted formerly, that approximate the medium duration of the period of incubation of the original infection. Again, it is not unusual to observe malarial fevers that relapse at intervals of about a month. But as far as I am aware the truth is less generally known about those fevers in which, after a long period of latency, relapses occur at certain seasons, so that it seems as though such relapses follow a definite law, for only recently this type of malarial recurrence has received attention. For instance, it is not uncommon to witness tertian malaria relapse in the spring, after remaining latent throughout the winter; and there are also estival fevers (estivo-autumnal infection, due to *P. falciparum*)* that, after remaining entirely dormant during the winter and spring, relapse at the beginning of summer.

For example, I had occasion to observe a patient, who had incurred fever in the summer of 1901 in Trinitapoli; after remaining entirely well throughout the winter and spring of 1902, he relapsed on the 25th of June of that year with a grave malarial attack, durir

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*Translator's parenthesis.

which asexual estivo-autumnal parasites were found in the blood, but no crescents. Of course, during the entire period of latency he had not exposed himself to the possibility of incurring a new infection. Nor would it be difficult for me to refer to other cases similarly well observed.

For some time various students of the factors concerned in malarial infections have supposed they could affirm that these estivo-autumnal relapses in the beginning of summer, after long latency, are due to a regular phenomenon that is manifested in a great number of sick persons, so much so that these observers believe these relapses may be due to accumulations of gametes from which anopheles are infected, thus producing again estivo-autumnal infections. In this way the new epidemic year is begun*. I cannot say, from my experience, if these facts to which I have just alluded possess very much importance from the epidemiological viewpoint, for, in truth, in malarial localities, it is very difficult to distinguish between a relapse and a reinfection in the inhabitants of these, and all criteria that have been suggested for the interpretation of the matter seem to me to be very arbitrary. The clinical course, for example, upon which some depend, is not to me a sure criterion; it is true that as a rule primary infections are graver, lasting longer than the attacks of relapse, but this happens in persons who hitherto have not had fever, while in a patient formerly a malarial subject a new infection cannot by any character be told from a relapse.

While I can, then, from my own experience affirm the occurrence of a relapse after a long period of latency, and at the beginning of the epidemic year, I cannot say if this happens with that regularity which would make the fact useful. If this be true, very great importance could be attributed to it from the epidemiological viewpoint. This point, and others, are questionable, and it is not essential to my purpose to go to the bottom of the matter, so that I limit myself to this brief notice.

As for the genesis of relapse, it is necessary to recognize that it is not yet known precisely in what forms the malarial parasites are found in the intervals of apyrexia between the febrile accesses, or to what biological property of these parasites may be attributed the fact that there are relapses of the fever.

All the hypotheses of the various authorities who admit that in man the gametes can multiply by means of parthenogenesis are worthy of being noted here. Although such a proposition may have been listened to in general with favor (some, for instance, believe that the epidemic year, at the onset of summer, begins with a group of relapses determined in old malarial cases by a "springtime parthenogenetic reproduction," as they say, of gametes), I maintain that such an hypothesis not only lacks a firm base of facts, but does not even lend itself to a satisfactory explanation of relapses.

The opinion that by the parthenogenesis of gametes relapses may be explained has as a positive foundation solely the observation of Schaudinn. (1) He, at the beginning of a relapse in a case of tertian malaria, saw and pictured a series of modifications in the macrogametes (female sexual parasites), which he thought he could interpret as similar to the forms of asexual multiplication. He reproduced in a plate the various forms that he found, placing them as in an ordinary developmental cycle. Then he adds that he has seen in other cases also some similar forms, but it is a fact that only once, and in a single patient, the whole series of forms in question has followed at the beginning of a relapse.* Notwithstanding this, he, after he had given a most accurate description in his report, expressed the *conviction* that relapses after long intervals owe their origin to macrogametes, which live a long time, and have the power, according to him, of undergoing a reversion to the form of schizonts (asexual parasites).

Although the publication of Schaudinn was put out in 1913, the process that he describes has not had even the most infrequent and insufficient confirmation by new observations.* The unconfirmed opinion based on that report has been listened to with favor, as though it were a datum of fact at this time unassailable.

I cite the observations of some Dutch authors, the only ones, as far as I know, who have also seen the forms described by Schaudinn.

Dr. G. I. Van der Hilst Karrewij (2) has taken

*The Italian school refers to the period of the annual increase and decline of malaria as the "epidemic year."—Translator's note.

up again the study of the disputed point, not having found other publications since those of Schaudinn. He in one case only of tertian malaria has found a series of forms that suggest to him a cycle of evolution in the macrogametes, precisely at the onset of an attack, and he describes the forms that he saw in the same manner as did Schaudinn. We have to do, then, with a simple confirmation of the observations of the latter, whose designs, it may be noted, are neater and demonstrate the points better than those that accompany the report of Karrewij. It should be noted that the patient with the tertian malaria who was the subject of Karrewij's observations already had had several attacks of fever when that one unexpectedly occurred at the beginning of which Karrewij found the forms described as demonstrating the parthenogenesis of the gametes.

Now, it is evident that, to explain the cause oi relapse, we would expect to find the said forms at the beginning of the first attack of the relapse itself, while everything tends to the belief that the following febrile attacks in a relapse are produced, as a rule, by the regular multiplication of the forms pertaining to the pyrogenous cycle. Therefore, the observation of Karrewij is not important concerning the origin of relapse, in the strict sense of the word, but would also lead to the belief that in the ordinary sequence of attacks the gametes might reproduce themselves either entirely or in company with the other forms of the parasites.*

Nor can I agree with Karrewij when he states that parthenogenetic division has been observed several times in crescents, and cites as confirmation the observations of Grassi, Mannenberg and Ziemann; these observations in my opinion, refer solely to isolated and incomplete reports, which hint at a transverse division of crescents, and they lack entirely value of demonstration in respect to the question which at present concerns us.

Similar observations to those of Karrewij in tertian malaria have been made, in the Dutch East Indies, by G. J. Merz and M. Bluml (2). There is this that is new in the results of these authors: in six preparations of blood from five persons sick with tertian malaria, they found forms that they interpret macrogametes in asexual division, and at the same time schizonts in division were also present. It is worthy of note that they had to do these cases with very heavy infections; so heavy were these that the authors found regularly double infection of the erythrocyte, more than once four tertian parasites in the same red blood cell, and in one as many as six schizonts. Schizonts in division were most plentiful, from 140 to 160 in a single preparation, nor were double infections of erythrocytes with gametes and schizonts lacking.

Now, to diagnose macrogametes in division, and to distinguish such from the numerous schizonts that were found in division at the same time in the preparations, the authors above mentioned relied on the description given by Schaudinn, and admitted without further proof that the distinctive characteristics of macrogametes in division had been previously ascertained and definitely postulated.

This simultaneous occurrence of macrogametes and schizonts in division, together with the fact that they were not able to state definitely in two of their cases whether a relapse or a reinfection were present, but rather had to admit the possibility of the latter supposition, naturally caused Merz and Bluml to think that the division of the macrogametes might not be the sole cause of the onset of relapse, as Schaudinn thought, but that to such division had been given too great value and broadness of meaning. But now, without following these authors in their attempts to give a satisfactory interpretation of the phenomenon, I shall content myself with noting that they have not seen the series of forms in question at the beginning of a relapse, and that, relying on the single observation of Schaudinn, they admit the relation between relapses and the multiplication of gametes. The same completeness, which constitutes the new and interesting data in their report, takes away, in respect to the question of relapse, its demonstrative value.

The observations of H. M. Neeb (3) are even less conclusive than those that I have mentioned. He refers in his work to having seen in tertian malaria some forms similar to those described by Schaudinn, and adds drawings and a description of three forms of parasites which he interprets as crescents in parthenogenesis. He found these in two preparations from a patient ill with tropical fever, but does not

*An excellent account of Schaudinn's work, with reproductions of his plates, is given in English by Deaderick, Practical Study of Malaria, 1909, p. 124, et seq. In the Journal of the Roval Army Medical Corps for December, 1909, Major W. S. Harrison gives an account of a similar phenomenon observed in the gametes in a case of relapse in tertian malaria, and his illustrations, which were made before he saw those of Schaudinn, are practically identical with the latter's, and with similar forms not infrequently seen here by me in tertian and quartan infections. Maj. Harrison does not commit himself, however, to a definite statement that his forms are undergoing parthenogenesis. It is also of interest to note that Captain C. F. Craig, U. S. Army Medical Corps, interpreted similar forms shown by me to him as the result of conjugating parasites. My personal opinion at the present time is that the forms I have observed are due to the atypical sporulation frequently seen in anemic blood, such as is common in those who suffer from relapse, but I am not prepared to make a definite statement at present. This information is appended solely for the guidance of those interested, and to confirm the statement that the forms described by Schaudinn actually occur, not in any way as a comment or a criticism on the views of Bignami, Schaudinn and others on the subject.—W. M. J.

*Dr. Bignami evidently is not familiar with the observation of Major Harrison, which should receive the credit due the careful statement of fact by an experienced and unprejudiced observer.—W. M. J.

*That is, Dr. Bignami questions whether the attack observed by Karrewij were really a relapse, for it followed unexpectedly other attacks of fever. Now, if this parthenogenesis actually has explanatory value in this instance, this value does not pertain to the cause of relapse, but merely shows that in the course of a malarial attack the phenomenon was observed. In other words, here the phenomenon means no more than ordinary asexual multiplication would mean, for there is no proof that it was part of a true relapse. (Translator's note.)

state how long the fever had lasted. It is, however, true, that the opinions expressed by various observers who examined Neeb's specimens were not in agreement as to two of the forms, although Prowazek interpreted them as parthenogenesis forms of crescents; Le Dantec showed the similarity of these same forms to the ordinary schizogony of estivo-autumnal parasites, and was reserved in his judgments. Others, of the Institute of Tropical Diseases in Hamburg, expressed the opinion that the forms were macrogametocytes (male crescents) in which the chromatin had already divided in the phase preceding the formation of the microgametes (flagella).

As for the third form in question, Neeb himself admits that he cannot give a precise opinion.*

The above facts, if I mistake not, are very far from being sufficient to convince us that relapses are due to schizogony of the macrogametes. They treat isolated observations which may, in some respects, demonstrate the possibility of parthenogenesis, but they do not permit us to affirm that such a process happens regularly at the beginning of a relapse. In fact, the proof of the constancy of such occurrence, and of the regular production of the phenomena in exact correspondence with the first access of relapse at long intervals, is lacking. Now it is not out of place to record that many students of malaria have patiently sought the phase of multiplication of crescents in the beginning of relapses, without success in demonstrating such a fact. Further, such researches have been made by Bastianelli and myself since the biological significance of crescents was first known; that is to say, when it seemed necessary that the phase of multiplication of crescents ought to exist in the blood of man. If all this is considered I believe that before firmly maintaining that Schaudinn is correct in his interpretation of the genesis of relapse,* we should take up new methodical researches, which at present are lacking, and that these should be carefully followed through, using staining methods best adapted, especially for estivo-autumnal gametes, which, as is well known, have morphological characteristics better differentiated and more easily distinguished than are those of the gametes of the other species of malarial parasites.*

There are very noteworthy facts, as to parthenogenetic reproduction, in other parasites; but, although analogy can be a guide in research, in this instance we cannot value it as a base for an hypothesis, when direct research in a well-known group of parasites does not furnish us with sufficient data to corroborate analogous findings in other groups. That the hypothesis (parthenogenesis) does not furnish an adequate basis of fact for the present conclusions, especially those for the estivo-autumnal species, is plain from the observations made many years ago by Bastianelli and myself on the behavior of crescents in human blood, observations that our recent researches have confirmed. So that, although it is admitted such a thing as the parthenogenetic reproduction of crescents in man may be possible, this hypothesis does not in any way help the interpretation of the cause of relapse, as is shown by the data just presented.

Nothwithstanding what is urged in favor of parthenogenesis as a cause of relapse, there are not infrequently recurrences of estivo-autumnal fever, at the beginning of which it is not possible to find crescents, even though splenic puncture be done, as has been noted in other works. In several instances, in the intervals of apyrexia between one relapse and the other, in persons who had chronic malaria, I have made examinations of the splenic juice without success in finding a crescent. On the

*In the Journal of Tropical Medicine and Hygiene, Volume XIII, No. 7, April 1, 1910, under the title of "The Parthenogenesis of the Female Crescent Body," Dr. Neeb gives in full detail the account referred to by Dr. Bignami, and also a plate showing the three forms in question, with tertian macrogametes in parthenogenesis also. Although Dr. Neeb had not seen the criticism of Dr. Bignami, as the two publications are of about the same date, he takes up in this article in great detail an explanation of the objections urged against his views by Dr. Bignami. (Translator's note.)

*I assert that this reserve should be maintained, although Ruge Handbuch der pathog. Microorganismen, Heraus von Kolle und Wassermen, Erganzungsband, Zweites H., page 416) considers the question of the pathogenesis of relapse now cleared up by the observation of Schaudinn on tertian malaria. (Author's note.)

*Such researches have been taken up this year in my laboratory. (Author's note.)

other hand, in quartan malaria, in which relapses often happen from month to month, gametes are extremely scarce, as has been shown by the negative results that have occurred repeatedly when it has been tried to infect anopheles mosquitoes with quartan parasites. Now it seems little likely that in such instances the cause of the continuance of the infection is due to forms of the parasites that occur very infrequently.

According to observed facts, it can be admitted that a portion of relapses are in connection with the recrudescence of pathogenetic reactivity of schizonts that carry on regularly their life cycle for a more or less lengthy period, without giving rise to fever. This is easily observed in quartan parasites, in whom the life cycle of the parasites can be followed in the finger blood to sporulation, and also through various generations, without the production of corresponding febrile attacks. In another work, in speaking of immunity, I have noted this fact, and I proposed to interpret it by admitting that the patients in question had acquired a transitory immunity against the fever producing activities of the hemosporidia. When this immunity is suspended, especially after some such occasional cause as chill or overwork, relapses follow.

Facts similar to these cited, such as the presence of parasites in the blood without accompanying febrile phenomena, have been observed recently by various authors, especially in the races resistant against malaria.

In such instances it cannot be doubted but that relapses may be due to the parasites of the pyrogenous cycle, which have been living in the blood without developing manifest pathogenic activity, such as the production of a febrile attack, on account of the particular condition of the patient at the time.

In considering the continued development of schizonts under such conditions, another group may be thought of; that which goes on in its cycle when cinchonization is not sufficiently prolonged and intense, such parasites escape the action of the remedy. Analogous examples are furnished in other infections, such as syphilis, in which a part of the virus escapes the specific cure, and by the cause of the later manifestations in the disease known as sleeping sickness, etc. Similarly the genesis of relapses at intervals rather short and more or less regular that present themselves frequently in those sick persons that are not treated adequately may be determined. As noted above, the period that intervenes between one group of febrile attacks and another sometimes has a duration that approaches that of the incubation period of the primary infection, and one may suppose that in the interval between these attacks there arises a progressive multiplication of the few residual parasites, until the quantity necessary for the production of the febrile attack is reached.

And there are other relapses, which come on after a more or less lengthy period of latency, which can be thought to have the same genesis. Indeed, there is nothing to compel us to admit that the residual parasites, which survive the action of quinine, and pass regularly and typically through their life cycle, ought to increase in a progressive manner by their multiplication. As is commonly known, quartan and tertian infections are seen, which, when not treated, go on monotonously for weeks and months without showing exacerbations, even not rarely diminishing in intensity of clinical symptoms, while not only does the number of parasites show no increase, but also may diminish in proportion to the lessening of the clinical symptoms. This may be explained by stating that not all of the young forms resulting from multiplication go on through a regular cycle of development. From these data we may suppose that a minimum quantity of parasites escapes the action of the specific remedy, and these follow their accustomed life cycle, without increasing in number, or perhaps without arriving at the limit of the quantity necessary to give fever until a long time has elapsed. Increase in number, with

rapid and progressive multiplication of the parasites can occur when the patient suffers from some debilitating cause that is the obvious occasion of the return of the fever. If this viewpoint be accepted the genesis of most relapses would be substantially identical with that to which I have just referred. In other words, it may be that in the intervals between relapses the usual forms of the pyrogenous cycle are found in the peripheral blood; or it may be that they cannot be found, yet relapses could always be due to the presence of such residual parasites, which, in the greater number of cases, are too few to be found in the regular examination.

But, although due consideration be granted to the foregoing data, there are yet certain facts for which a satisfactory explanation has not yet been given. Thus it is not easy to understand why, if, in the intervals of apyrexia, quinine is administered every day and in large doses, still, in a certain number of cases, relapses occur. I repeat, this is not easily understood, if it is admitted that in the blood in minimum number there are the same forms that develop during the febrile periods, and that in these it is not possible to demonstrate any biological change, unless we wish to suppose that during the periods of latency the parasites are more resistant to quinine, and further, that during the fever certain modifications occur, by which the parasites may be made more sensible to the action of the drug, which facts certainly cannot be denied *a priori*.

More than once I have administered the sulphate of quinine in doses of a gramme a day, and even in larger doses, to persons who had chronic malaria, and I have seen a relapse occur, with estivo-autumnal parasites in the peripheral blood a few days after the withdrawal of the remedy. On the other hand, I have found out that, in cases of experimental malaria, which were energetically treated after the first access of fever, relapses were reduced to a minimum, and sometimes entirely suppressed. Moreover, it is a matter of common knowledge that the sooner after the manifestation of fever treatment is begun the more easily the physician can control the infection; while infections that have run for some time are more rebellious to treatment.

Nor is it easy to understand, granted that relapses are due to the mechanism to which I have referred above, the relapses due to different species of the parasites. For example, cases are not rare, when, after a series of estivo-autumnal relapses during the autumn and winter and apparently cured, in the spring a relapse of ordinary tertian occurs under circumstances of environment that make it possible to exclude a reinfection with this parasite. Why have the parasites of tertian fever resisted the action of the remedy that has conquered even the estivo-autumnal parasites, if the former occurred in the blood in the well-known forms of the pyrogenic cycle?

These considerations, and others analogous to them, caused me some time ago to formulate an hypothesis that should depend on a morphological basis. According to this some spores (monogenic sporozoites) might be deposited in the internal viscera, where, making a membrane for themselves, they could change into resisting forms and could provide for a continuance of the infection.

It is well known that not all of the parasites that result from sporulation at the beginning of a febrile attack go on through the developmental cycle. In fact, and this is especially demonstrated in quartan infections, if all of the merozoites resulting from multiplication of the parasites should develop regularly the number of parasites in successive attacks would increase in a definite proportion, which is not so. Some of these merozoites and also entire fission forms are deposited in the internal viscera, especially in the spleen and in the bone marrow, where, and this rests the hypothesis, they may be able to convert themselves into resistant forms.

This hypothesis was adopted, in my opinion, to explain not only the facts previously re-

ferred to, but also particularly the fact that relapses are less probable and less numerous in direct proportion to the number of febrile attacks that occurred before the exhibition of a rigorous and methodical quinine treatment.

But inasmuch as more accurate researches undertaken whenever the opportunity offered, especially on the spleen and bone marrow, in cases of chronic malaria, have not given me a positive result; that is to say, such researches have failed to demonstrate the supposed resisting forms as morphologically differentiated, nor have others had better success, it is now my opinion that the said hypothesis ought to be abandoned, at least provisionally,* the more so since it is possible to substitute for it another that has as a basis the support of analogy. I refer to the observations made in the past few years in the school of Ehrlich concerning the behavior of trypanosomes when acted upon by various remedies.

As is known, in the Institute of Frankfort (4), it has been demonstrated that the insuccess of the protracted treatment of trypanosomiasis over a long time, and with various chemical agents, depends upon this fact; that there is formed little by little *varieties* of trypanosomes resistant against the said agents. Thus Ehrlich, with Browning and Rohl, has obtained a strain of trypanosomes resistant against fuchsin and against a series of other toxic substances (tri-phenyl-methane staining substances), a strain resistant against trypan-red and allied substances—trypan-blue and trypan-violet—and finally, a strain resistant against arsanil.

In rats resistance against atoxyl is observed as a rule after a long time, but Ehrlich has had cases in which it could be demonstrated after fourteen days. This observation is of importance, because it gives us a possibility of explaining by this resistance the negative results that occur in the treatment of sleeping sickness, notwithstanding the administration of the remedy for a long while.

Once acquired, this property of resistance can remain unchanged for long periods. Thus, the strain resistant against arsanil (arsanil fast) has been passed 300 times through normal animals, which requires about 700 days, and despite this long time it has preserved intact its resistance; that is to say, the resistance is hereditary.

Ehrlich has carried the strain resistant against atoxyl (atoxyl fast) through more than 125 changes without observing any diminution in its powers of resisting the drug.

Also of importance is the fact that the resistance of these types of strains is specific. So that the strain resistant against fuchsin is not resistant against atoxyl and trypan-red and *vice-versa*. The resistance is lost if chemicals other than those of a particular group are used.

Nor are facts analogous to the preceding lacking.

Thus Franke, in Ehrlich's laboratory, has found that there exists types of strains of parasites resistant against the protective substances formed during the course of an infection.

Levaditi has observed the same fact with regard to the spirilla of relapsing fever.

To the same group of facts belong the observations of Effront, who many years ago succeeded in obtaining protozoa resistant to hydrofluoric acid, and biologically endowed with properties different from those of the normal protozoa; and also he showed that these protozoa preserved through many generations this specific resistance to poison, acquired by adaption.

It is a question, then, according to Ehrlich, of a general law. This is of the greatest im-

*It would be useful to study anew the question, applying to the examination of the blood-making organs of patients with relapsing malaria, who die from intercurrent diseases such as pneumonia, all the new methods introduced in the last few years in histological technique and in the recent study of protozoa. It is noted, in view of the necessity of such study, that I, *apropos* of my old hypothesis, do not express myself as abandoning it decisively. (Author's note.)

portance because of the fact that the acquired modification (resistance or immunity)* results from hereditary properties.

Ehrlich knows of one case communicated by Professor Plimmer, with respect to a strain of trypanosomes from a patient with sleeping sickness, who had been treated for a long time with arsanil, which strain, when experimentally introduced into animals, showed itself very resistant to that substance (arsanil fast).

I shall add this fact, shown by the researches of Morgenroth and Halberstaedter (5), that there is a similar connection between quinine and trypanosomes. These authors, who sought to demonstrate by research if quinine would exercise a prophylactic action in experimental infections with trypanosomes, were of the opinion that they had demonstrated that the drug had such an action (the quinine acted on the trypanosomes by inhibiting their reproductive activity) and they admitted the possibility that, in latent trypanosomiasis, there can be established a kind of habituation of the organisms to quinine, (a certain quinine fast property of the trypanosomes).

I have cited at length the results of the above studies in order to set forth what seems to be justified in the actual state of our present knowledge, a similar hypothesis to explain the obstinate resistance to quinine that is presented in relapsing malaria, especially in the clinical cases of chronic malarial infection.

Such resistance is common knowledge of physicians who practice in malarial communities. And it is on account of this resistance that not seldom patients refuse to continue taking quinine, because they do not feel in a more manifest manner the beneficial effects of the drug. Thus they prefer to have recourse to the patent medicines which inundate the market and find ready believers in their virtues; especially when the name does not indicate clearly the quinine content; so that the thoughtless do not realize that, under a different label, they are continuing to take the valuable alkaloid.*

I have already stated the results of my experience. Not only did the administration of quinine by mouth every day in large doses fail, in some cases, to eliminate subsequent relapse, but the same insuccess can follow energetic treatment by hypodermic injections. Not to limit myself to the citation of my own experiences, I shall record, for example, a case described by Torti and Angelini (6), who in this instance injected hypodermically every day a gramme of quinine for fifteen days; then gave the remedy by mouth for about a month, and, notwithstanding this, observed a relapse. They then gave hypodermic injections for fifteen days more (half a gramme a day), and the day after the suspension of the remedy, they observed fever with the finding of parasites in the peripheral blood.

But it would be useless to cite further individual observations, so well is known the resistance which not rarely cases of chronic malaria offer, whether or not febrile manifestations are shown, to energetic and continued quinine treatment.

I have already noted the facility with which cases of experimental infection from anopheles can be controlled, if, as soon as the fever

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*Translator's parenthesis.

Although the authorities mentioned, as occasion has offered, in their experimental researches have obtained strains of maximum resistance, we must not expect, according to Ehrlich, that the same grade of resistance in the course of a drug treatment will be obtained in man as is obtained in animals, for in man strains of medium resistance (half fast) will follow habituation of parasites to a drug; under the action of atoxyl in suitable doses, trypanosomes become scarce, but after a certain time they reappear, whence the difficulty of treating these cases.

The experience that we possess in regard to such cases (those in which such "half fast" parasites have been transferred from man to animals)* is very scanty.

*Translator's parenthesis.

*Evidently the sale of "sure cures" for fever and chills, which are guaranteed not to contain quinine, is not confined to the southern part of the United States. One of these was analyzed some years ago by me. The label stated that it was guaranteed not to contain quinine, but none the less five grains of the drug to the dose was found in the preparation.—W. M. J.

is manifest and the parasites appear in the blood prompt and continued treatment is instituted. From the facts of which I have knowledge although they are not numerous, I am of the impression that infections brought about by injection of malarial blood do not yield so easily. This difference perhaps could depend on the fact that in this latter instance the injected parasites were already habituated in the first human host to the action of quinine, to which, in the schizont stage, they had already become resistant.

All these data can be interpreted by the hypothesis that I shall propose as most in conformity with our actual knowledge. Thus, I admit that certain malarial parasites under the action of quinine, in some cases, are selected to form resistant strains, whence the difficulty of a radical cure in such fevers that relapse obstinately. It is not possible to say certainly, with any approximation, to what extent this can be verified. But resistant cases, although rare, are evidently those which should be most considered in regard to prophylactic measures, because it is these which are largely responsible for the persistance of infection and its continued spread by such cases that are able to be up and around.

There are also facts which cause me to think that there may be some strains of parasites endowed orginally with great resistance to quinine. For example, several times Marchiafava and I have seen at autopsy cases of pernicious malaria very rich indeed in parasites accumulated in the vessels of the central nervous system, the spleen, the liver, the bone marrow, etc., in spite of an energetic quinine treatment for more than two days. Since these were recent infections, in these cases it does not seem admissable that the resistant strain, so to speak, was selected in consequence of the use of the alkaloid. With these may be contrasted those pernicious cases in which the quinine used in large amounts brings about the complete destruction of the parasites; notwithstanding which death supervenes, seemingly in consequence of alterations in the viscera secondary to the parasitic invasion, and at autopsy no parasites are found, or perhaps a few forms after accurate examination (7).

The conclusion that follows from all this has not to do, certainly, with confidence in the efficacy of quinine treatment, as every one knows that by persistence in proper treatment the infection can be conquered; but it concerns the treatment of malarial patients as rapidly as possible, intensifying our efforts at the beginning of the malady, inasmuch as a complete and rapid cure is the more probable in proportion to the promptness of the administration of the remedy.*

And it is almost useless to add that the formation of strains resistant or semi-resistant (half fast) to quinine is a matter that does not admit of experimental proof, such as has been shown with trypanosomes. Human malaria not being transmissible to animals, it would be necessary to inoculate a healthy person with the blood from a resistant and relapsing case, in order to see if the same biological properties of the parasites would be recognizable in the inoculated person. But for obvious reasons, this is not practicable, nor is the solidity of the hypothesis affected thereby, so many are the observations that sustain it.

It seems to me possible to infer in due course concerning the genesis of relapses:

1. That the data presented hitherto do not permit, as far as our present knowledge is of avail, that the reports of relapses due to persistence of the macrogametes are parthenogenetic multiplication of these can be affirmed with certainty.

2. That in all probability relapses, whether at short or long intervals, or whether separated by lengthy periods of latency, should be considered from a single viewpoint; that is to say, as having the same genesis, depending on the persistence of the pyrogenous cycle.

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*Naturally one can come to practically the same conclusion, if one admits that the genesis of relapses is due to parthenogenesis of the macrogametes. Indeed, the peculiar resistance of these forms to the action of quinine is common knowledge. (Author's note.)

In one group of relpases the parasitic material that maintains the infection is represented by a minimum quantity of forms of the ordinary fever producing cycle, often recognizable by an accurate microscopical examination, at least at some time in the course of the infection, which forms for a long time cannot attain the quantity or the virulence necessary to cause fever. Especially in those cases in which a series of relapses occur at longer or shorter intervals without quinine treatment, one should keep in mind the possibility that after a series of febrile attacks the organism acquires a certain immunity in respect to the pyrogenic action of the parasites; which immunity being transitory, as happens in other infections, it is attenuated or ceases after a certain period of apyrexia; whence the onset of relapse.

But there is also a group of relapses, in which the material that maintains the infection during the period of latency, is represented by forms resistant to quinine, due to a process of selection under the action of the alkaloid, as occasion offers; it is not necessary to suppose that such forms differ morphologically from others as I, myself, more than once,* have also thought.

Such modifications in the biological properties of the parasites are admitted by me, on account of the difficulty that is encountered in trying to explain all the facts regarding relapses, and especially the inefficacy of quinine treatment during long periods of latency accompanied by perfect health, and also the relation that exists on the one hand between the frequency and the obstinacy of relapses, and the number of febrile attacks that occur without cure or with only an incomplete therapeutic success on the other.

If the facts that I have demonstrated are admitted, so that it is conceded that occasionally there occur strains truly resistant to quinine, it is reasonable to think that similarly there are found with a certain frequency in chronic cases of malaria strains of parasites endowed with a medium resistance against the alkaloid, analogous to what Ehrlich believes to happen with the trypanosomes in sleeping sickness in respect to arsenical preparations; and though in such malarial cases treatment not sufficiently energetic and protracted will bring about a practical absence of parasites from the blood, it will not avoid a return of the fever and parasites after a longer or shorter time.

*I was formerly of the opinion that all forms of the parasites, except, of course, the gametes, were equally affected by the action of quinine when the drug was properly administered, and so expressed myself in a paper on quartan malaria. But since reading Dr. Bignami's article, I have made a more careful study, using quinine in varying doses, and I can confirm Dr. Bignami's statement, that there are forms of the ordinary asexual cycle that are resistant to quinine, and do not differ morphologically from the normal asexual parasites. If quinine be given, say in tertian infections, in doses of three grains three times a day, many of the parasites can be observed undergoing the changes accurately described by Captain C. F. Craig as occurring under the influence of the drug, but many more do not show such changes. In proportion as the dosage is increased, fewer normal parasites are found, but prolonged search will nearly always reveal such normal parasites, and these, as long as they escape the action of quinine, certainly could renew the infection, as Dr. Bignami believes.—W. M. J.

Note.—The construction of sentences in Italian differs so markedly from English composition that in many instances it has been necessary to recast entire paragraphs. I have, however, tried to follow as faithfully as possible the style and expression of Dr. Bignami, and any lack of clearness or fault of rhetoric should be attributed to the shortcomings of the translator, and not to the author, whose paper in the original is a model of clearness and good style.—W. M. J.

REFERENCES.

1. J. Schaudinn: Studien uber Krankheitserregende Protozoen. See the chapter, Ruckbildung und Schizogonie der Markrogameten bei einem Recidiv. Arbeiten und dem Kaiserl. Gesundheitsamte, 1903. pages 230 et seq.

2. Geneeskundig Trijdschritt voor Nederlandsch-Indie, 1908.

3. Geneeeskundig Tijdschritt voor Nederlandsch-Indie, 1909.

4. Ehrlich: Chemotherapeutische Trypanosomen-Studien, Liepzig, 1909.

5. Zur Kenntniss der Chininwirkung. Berl. klin. Woch, 1910, n. 14.

6. Infezione malarica cronica con i sintomi della sclerosis a placche. Reform Merica, 1899.

7. See Marchiafava e Bignami, L'infezione malarica, 1902. (This work, which is beyond any question the most complete published on malaria and its complications, is printed in English in the Ninteenth

Volume of the Twentieth Century Practice of Medicine, New York, William Wood & Co. I earnestly recommend anyone interested in the study of malaria to consult this volume before advancing any personal observations. I speak from personal experience.—W. M. J.)